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PANCREAS, BILIARY TRACT, AND LIVER

Clinical Features of COVID-19-Related Liver Functional Abnormality

Zhenyu Fan,[*,a] Liping Chen,[*,a] Jun Li,[*] Xin Cheng,[*] Jingmao Yang,[*] Cheng Tian,[*] Yajun Zhang,[*] Shaoping Huang,[*] Zhanju Liu,[‡] and Jilin Cheng[*]

[*]Department of Gastroenterology and Hepatology, Shanghai Public Health Clinical Center, Fudan University, Shanghai, China; and [‡]Department of Gastroenterology, The Shanghai Tenth People's Hospital of Tongji University, Shanghai, China

BACKGROUND & AIMS: **Some patients with SARS-CoV-2 infection have abnormal liver function. We aimed to clarify the features of COVID-19-related liver damage to provide references for clinical treatment.**

METHODS: **We performed a retrospective, single-center study of 148 consecutive patients with confirmed COVID-19 (73 female, 75 male; mean age, 50 years) at the Shanghai Public Health Clinical Center from January 20 through January 31, 2020. Patient outcomes were followed until February 19, 2020. Patients were analyzed for clinical features, laboratory parameters (including liver function tests), medications, and length of hospital stay. Abnormal liver function was defined as increased levels of alanine and aspartate aminotransferase, gamma glutamyltransferase, alkaline phosphatase, and total bilirubin.**

RESULTS: **Fifty-five patients (37.2%) had abnormal liver function at hospital admission; 14.5% of these patients had high fever (14.5%), compared with 4.3% of patients with normal liver function ($P = .027$). Patients with abnormal liver function were more likely to be male, and had higher levels of procalcitonin and C-reactive protein. There was no statistical difference between groups in medications taken before hospitalization; a significantly higher proportion of patients with abnormal liver function (57.8%) had received lopinavir/ritonavir after admission compared to patients with normal liver function (31.3%). Patients with abnormal liver function had longer mean hospital stays (15.09 ± 4.79 days) than patients with normal liver function (12.76 ± 4.14 days) ($P = .021$).**

CONCLUSIONS: **More than one third of patients admitted to the hospital with SARS-CoV-2 infection have abnormal liver function, and this is associated with longer hospital stay. A significantly higher proportion of patients with abnormal liver function had received lopinavir/ritonavir after admission; these drugs should be given with caution.**

Keywords: Prognosis; Liver Injury; ALP; Antiviral Drug.

In December 2019, a novel coronavirus was identified as the pathogen to cause pneumonia in Wuhan, China, which was temporarily named as 2019-nCoV by the World Health Organization.[1,2] On February 11, 2020, based on the phylogeny, taxonomy, and established practice, 2019-nCoV was officially named as SARS-CoV-2,[3] and the disease caused by SARS-CoV-2 was named as COVID-19.[4] SARS-CoV-2 can be transmitted from person to person through respiratory droplets and close contact, posing a huge public health challenge.[5] So far, there were more than a million confirmed cases in 181 countries and regions around the world.[6]

The main manifestations of SARS-CoV-2 infection include fever, dry cough, weakness, and breathing difficulty. Abnormality in liver function tests has been reported; almost one-half of patients experience different degrees of liver test abnormalitities.[7,8] According to a recent study using single-cell RNA sequencing, angiotensin-converting enzyme 2 was highly expressed not only in type II alveolar epithelial cells, but also in bile duct cells.[9] Importantly, recent studies confirmed that angiotensin-converting enzyme 2 receptor is the cell entry receptor of SARS-CoV-2.[10] All these findings suggest that SARS-CoV-2 may infect the bile duct cells and cause the abnormal liver function in these patients. However, alkaline phosphatase (ALP), the bile duct

[a]Authors contributed equally.

Abbreviations used in this paper: ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; LDH, lactate dehydrogenase.

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injury marker, is not specific to COVID-19.[7,8] A recent study reported that moderate microvascular steatosis and mild lobular and portal activity were present in liver biopsy specimens, indicating that the liver injury could be caused by either SARS-CoV-2 infection or drug-induced liver injury.[11] Currently, however, there are no data to determine whether abnormal liver function in COVID-19 patients is caused by drug use or not. Given the highly contagious and pathogenic nature of SARS-CoV-2 and the high incidence of liver damage, an in-depth evaluation of liver function in COVID-19 patients is urgently warranted.

In this study, we retrospectively investigated the changes in liver function tests in SARS-CoV-2-infected patients from a single center in Shanghai, China, and compared the clinical features, medications, and length of stay of COVID-19 patients with versus those without liver damage. The purpose of this study is to clarify the clinical features of COVID-19 patients with abnormal liver function, evaluate the association between current medications and liver damage, and provide a reference for clinical treatment of patients with COVID-19.

What You Need to Know

Background

Some patients with SARS-CoV-2 infection (COVID-19) have abnormal liver function, but little is known about the features in these patients.

Findings

More than one third of patients admitted to the hospital with SARS-CoV-2 infection have abnormal liver function; significantly higher proportions of patients with abnormal liver function are male and have high fever and prolonged length of stays. 48.4% of patients with normal liver function had abnormal liver function test after admission, with a higher proportion of receiving lopinavir/ritonavir.

Implications for patient care

Lopinavir/ritonavir should be given with caution in patients with COVID-19.

Methods

Study Design and Participants

From January 20, 2020, to January 31, 2020, a total of 148 consecutive patients were admitted and treated in the Shanghai Public Health Clinical Center affiliated to Fudan University (the designated hospital for infectious disease by the Chinese Center for Disease Control and Prevention in the Shanghai area), all of which were confirmed cases of COVID-19. The clinical criteria of diagnosis and discharge were as per the standards for "Diagnosis and Treatment Scheme of New Coronavirus Infected Pneumonia" (trial version 6).[12] All cases had a history of exposure and most had clinical manifestations including fever or respiratory symptoms. All patients were diagnosed after examination of SARS-CoV-2 RNA by reverse transcriptase polymerase chain reaction. Follow-up for this report ended on February 19, 2020. This study was approved by the Ethics Committee of the Shanghai Public Health Clinical Center (2019-S047-02; review date, January 13, 2020) and was exempted from the need for informed consent from patients.

Data Collection

The medical records of 148 patients were collected and examined by the research team from the Department of Gastroenterology and Hepatology, Shanghai Public Health Clinical Center, Fudan University. Epidemiological, clinical, laboratory characteristics, and treatment and outcomes data were acquired by the hospitalization management system.

Laboratory Examination

Sera were harvested from all confirmed patients after an overnight fast. All laboratory data were obtained on the day of serum collection. Laboratory examination was conducted every 3 days. Peripheral leukocyte count, lymphocyte absolute value, erythrocyte sedimentation rate, procalcitonin, and liver functions including alanine aminotransferase (ALT; 9–40 U/L), aspartate aminotransferase (AST; 13–35 U/L), γ-glutamyltransferase (7–45 U/L), ALP (35–100 U/L), and total bilirubin (3.4–20.5 μmol/L) were routinely measured using standard methods. The phenotypic analysis of lymphocytes ($CD4^+$, $CD8^+$, $CD3^+$ T cells) in peripheral blood was performed by a flow cytometry (BD Biosciences, San Diego, CA). We defined abnormal liver function as any parameter (ALT, AST, ALP, gamma lutamyltransferase and total bilirubin) more than the upper limit of normal value.

Therapeutic Strategies

All patients rested in bed and received supportive treatments, including fluid supplementation and maintenance of electrolyte and acid-base homeostasis. Vital signs and finger oxygen saturation were closely monitored, and oxygen therapy was given to patients with hypoxemia. Because there was no accepted antiviral treatment regimen, patients were treated with lopinavir/litonavir, umifenovir, and darunavir. There was no standard guidance on drug choice. Antibiotics were used if needed and this decision was based on health care providers' discretion.

Table 1. Clinical Characteristics of 148 Patients Infected With SARS-CoV-2

		Liver function		
	All (148)	Abnormal (55)	Normal (93)	*P* value
Age	50 (36 –64)	52 (37–65)	50 (36–63)	.5829
Sex, n (%)				
Female	75 (50.7)	14 (25.5)	61 (65.6)	< .0001
Male	73 (49.3)	41 (74.5)	32 (34.4)	
Signs and symptoms at admission, n (%)				
Fever	127 (85.8)	48 (87.3)	79 (84.9)	.6951
Cough	67 (45.3)	25 (45.5)	42 (45.2)	.9724
Expectoration	38 (26.7)	14 (25.5)	24 (25.8)	.9622
Diarrhea	6 (4.1)	1 (1.8)	5 (5.4)	.4124
Nausea and vomiting	3 (2.0)	1 (1.8)	2 (2.2)	1
Asymptomatic	5 (3.4)	2 (3.6)	3 (3.2)	1
With other liver diseases	9 (6.1)	4 (7.3)	5 (5.4)	.6409
Temperature (°C), n (%)				
≤37.2	21 (14.2)	7 (12.7)	14 (15.1)	.6951
37.3–38	70 (47.3)	24 (43.6)	46 (49.5)	.4927
38.1–39	45 (30.4)	16 (29.1)	29 (31.2)	.7892
≥39.1	12 (8.1)	8 (14.5)	4 (4.3)	.0274
Onset of symptom to admission, *d*	5 (3–7)	5 (3–8)	5 (3–7)	.32
Laboratory examination, median (interquartile range)				
WBC (*10-9/L)	4.635 (3.62–5.7)	5.04 (3.89–5.72)	4.35 (3.55–5.6)	.1033
Lymphocytes	1.115 (0.76–1.51)	1.05 (0.69–1.57)	1.2 (0.785,1.5)	.3208
PCT	0.03 (0.02–0.06)	0.06 (0.03–0.09)	0.02 (0.02–0.05)	< .0001
CRP	17.75 (8.7–32.38)	25 (12.68–42.18)	13.2 (7.9–25.83)	.0105
ESR	50 (32–84)	70 (36–86)	47.5 (31.25–83.5)	.4181
$CD4^+$ T, *cell/μL*	407 (261–619.8)	397 (216–591)	408 (290–628)	.3
$CD8^+$ T, *cell/μL*	260 (163.3–384.5)	225 (148–364)	265 (181.5–403)	.1227
$CD3^+$ T, *cell/μL*	710 (494.5–1024)	638 (424–1056)	752 (546–1024)	.2066
LDH	224.5 (193–283.8)	257 (227–369)	207 (186–243)	< .0001
Clinical outcomes, n (%)				
Severe/critically ill	10 (6.8)	5 (9.1)	5 (5.4)	.3843
Cured and discharged	92 (62.2)	34 (62.8)	58 (62.4)	.9471
Death	1 (0.7)	1 (1.8)	0	.3716

CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; LDH, lactate dehydrogenase; PCT, procalcitonin; WBC, white blood cell count.

Statistical Analysis

Continuous measurements were compared by Student *t* test or Mann-Whitney *U* test, which with normal distribution were presented as mean ± standard deviation, whereas the abnormally distributed measurements were presented as median (interquartile range), respectively. The categorical variables (shown by percentage) were compared by using chi-square analysis and Fisher exact test. $P < .05$ was determined as with statistically significant differences. Statistical analysis software Prism 6 (GraphPad, La Jolla, CA) was used for all analyses in this study.

Results

Clinical Characteristics of Patients Infected With SARS-CoV-2

Up to January 31, 2020, a total of 148 cases with COVID-19 were admitted to the Shanghai Public Health Clinical Center, including 73 (49.3%) females and 75 males (50.7%). The average age of the patients was 50 years (36–64). Ninety-two of the 148 cases were discharged from the hospital by February 19th, and 1 died. The deceased patient was critically ill on admission with complex underlying diseases. On day of admission, the patient was treated with antibiotics, antivirals, and mechanical ventilation and other rescue measures. Elevated levels of AST (48 U/L) and continuously elevated LDH were observed in the patient on the next day, and reduced glutathione was used to protect the hepatic function. Unfortunately, the patient died of respiratory failure on Day 3. Patients in this cohort had clinical manifestations of fever (85.8%), cough (45.3%), and expectoration (26.7%) on admission. The clinical and laboratory features of patients with and without normal liver tests are shown in Table 1.

Liver Function and Medications in COVID-19 Patients

There were 55 patients (37.2%) with abnormal liver function tests on admission (Supplementary Figure 1*A*),

Table 2. Medications Used by COVID-19 Patients Before Admission

Liver function	N	Antibiotics	Antiviral	Arbidol	Oseltamivir	Antipyretic analgesics	No medication
Abnormal	55	19 (34.5)	12 (21.8)	2 (3.6)	10 (18.2)	3 (5.5)	27 (49.1)
Normal	93	31 (33.3)	27 (29.0)	11 (11.8)	17 (18.3)	11 (11.8)	42 (45.2)
P value		.8802	.3357	.1325	.9881	.254	.6433

NOTE. Values are number (percentage).

including elevated ALT (n = 27; 41–115 U/L), AST (n = 32; 37–107 U/L), γ-glutamyltransferase (n = 26; 48–159 U/L), ALP (n = 6; 102–144 U/L), and total bilirubin (n = 9; 21–46.6 μmol/L). As shown in Supplementary Figure 1*B*, the proportion of patients with elevated AST, ALT, γ-glutamyltransferase, total bilirubin, and ALP was 21.6%, 18.2%, 17.6%, 6.1%, and 4.1%, respectively. The medications of COVID-19 patients before admission included antibiotics (levofloxacin, azithromycin, cephalosporin), antiviral drugs (umifenovir, oseltamivir, acyclovir), and conventional antipyretic drug (ibuprofen). There was no statistical difference in prehospital treatment between the groups with or without liver test abnormalities (Table 2).

Of 45 patients with normal baseline liver function tests, 48.4% developed liver functional abnormality mean 7 (range, 4–11) days after admission. Of these, 18 had elevated bilirubin and the peak occurs on the fifth day (range, 4–12) following hospitalization. In total, 27 patients had elevated liver enzymes and the peak occurs on the 10th day (7–12) after hospitalization. The trajectory of liver enzymes in patients with abnormal liver function after admission was shown in Supplementary Figure 2. More patients with abnormal liver function (57.8%) received treatment with lopinavir/ritonavir compared with those with normal liver function (31.3%; $P = .01$) (Table 3).

Association Between Abnormal Liver Function and Overall Prognosis

Ninety-two (62.2%) patients were discharged from hospital as of February 19, 2020, including 34 cases with abnormal liver function before admission, 24 cases with abnormal liver function during hospitalization, and 34 cases with normal liver function during the stay in hospital. Of note, we found that baseline abnormal liver function was associated with prolonged hospital stay, whereas abnormal liver function during admission had little effect on the length of hospital stay (Table 4).

Discussion

In the current study, nearly half of the patients in this study were older than 50 years old, which is consistent with the previous report.[13] Half of the patients were men, whereas another study including 72,314 cases demonstrated that COVID-19 was more common in men than women.[14] In total, 85.8% of patients presented with fever; this estimate is similar to 83% to 98.6% in other reports.[2,7,8] There were 5 asymptomatic patients in our study, who were hospitalized after close contact with confirmed cases, and then diagnosed with COVID-19. Recently, an asymptomatic carrier was reported to transmit SARS-CoV-2 to 5 other persons.[15] Undoubtedly, asymptomatic patients increase the challenge in the prevention of COVID-19 infection.

Notably, 37.2% of patients on admission had abnormal liver function. Similar to previous studies, ALP elevation was the less common compared with abnormalities of the other liver enzymes.[16] Although angiotensin-converting enzyme 2 is highly expressed in bile duct cells, recent work suggest that SARS-CoV-2 infection does not cause bile duct injury.[9] In contrast, elevated markers of liver cell injury (ALT, AST) are more common. Approximately 1 in 5 patients in this study had elevated ALT or AST, which is slightly lower than the estimates in earlier studies.[2,8] Moreover, the levels of elevated ALT and AST were generally not high in our study, indicating the COVID-19-related liver injury may be relatively mild. These findings are consistent with the previous research.[7] We found that abnormal liver function was more common in men, although the mechanism is unclear. We also found that patients with abnormal liver function had higher inflammatory indexes, such as elevated C-reactive protein and procalcitonin, and more

Table 3. Medications Used by COVID-19 Patients After Admission

Liver function	N	Antibiotics	Antiviral	Arbidol	Lopinavir/ritonavir	Darunavir
Abnormal	45	21 (46.7)	39 (86.7)	22 (48.9)	26 (57.8)	5 (11.1)
Normal	48	15 (31.3)	36 (75.0)	26 (54.2)	15 (31.3)	8 (16.7)
P value		.13	.15	.6108	.01	.44

NOTE. Values are number (percentage).

Table 4. Hospital Stays of Patients, Stratified by Normal/ Abnormal Liver Function

Timeline	Hospital stays/recovery time days (cases of discharge)		
Liver function	Before admission	After admission	Total
Abnormal	15 (13–18) (34)	14.85 ± 5.54 (24)	15.09 ± 4.79 (58)
Normal	14 (9.75–16) (58)	12.76 ± 4.14 (34)	12.76 ± 4.14 (34)
P value	.04	.1088	.0206

NOTE. Hospital stays/recovery time: from admission to discharge (recovery).

likely to have fever, which may be related to the immune response after virus infection. Studies have found elevated transaminase is more common in patients with severe pneumonia, which is suspected to be associated with inflammatory cytokines,[2,7] but it cannot explain there are also abnormal liver function parameters in mild patients.

There are similarities between the SARS-CoV-2 and SARS-CoV outbreaks. In the autopsy analysis of patients who died of severe acute respiratory syndrome,[17,18] liver tissue showed fatty degeneration and central lobular necrosis; SARS-CoV was also detected in the liver.[19] Thus, there is a reason to believe that SARS-CoV-2 can also attack the human liver.

It is worth noting that LDH was higher in patients with abnormal liver function than in patients with normal liver function. Also, a high level of LDH was found in the patient who died of respiratory failure in our study. The levels of LDH in the patients with severe acute respiratory syndrome and Middle East respiratory syndrome are also increased.[20,21] and can be seen as an independent risk factor for severe acute respiratory syndrome.[20] Whether LDH can be used as an early alarm feature for COVID-19 needs further analysis.

Although there are also serious liver injuries in previous reports, the concomitant chronic liver diseases could not be excluded.[8] Nine patients had other chronic liver diseases in our study, but there was no statistical difference in the proportion of patients with chronic liver diseases between the abnormal and the normal liver function group.

Because no effective antiviral drug for COVID-19 is available, symptomatic and supportive treatments are crucial. Many patients were treated with antiviral and antipyretic drugs. However, both antiviral drugs and acetaminophen have adverse reactions, including liver injury.[22–24] In our study, the drugs used by patients before admission are mainly antibacterial drugs (including moxifloxacin, cephalosporins), antiviral drugs (umifenovir, oseltamivir, acyclovir), and antipyretic drugs (eg, acetaminophen). We analyzed the prehospital medications and found that there was no statistical difference between the 2 groups. Therefore, we believe that the onset of liver function damage of COVID-19 patients had nothing to do with the medications. After admission, several patients with normal liver function developed liver functional abnormality. We found that of the proportion of patients who were treated with lopinavir/ritonavir was significantly higher in the group with than the group with sustained normal liver function. In another study from our hospital, lopinavir/ritonavir did not enhance the clearance of SARS-CoV-2.[25] For this reason, we would not recommend lopinavir/ritonavir as a treatment for COVID-19, even in mild patients with normal liver function. More studies are needed to further evaluate the risks and benefits of lopinavir/ritonavir in patients with COVID-19. Notably, the length of stay in patients with abnormal liver function on admission was longer than that in cases with normal liver function.

Our study has several limitations. This study was retrospective, and some cases had incomplete documentation for the history of present illness. Moreover, we examined the association between COVID-19 and abnormal liver function and cannot demonstrate causality. Further studies are needed to corroborate the pathogenic mechanism.

In conclusion, abnormal liver tests are common in COVID-19 patients. SARS-CoV-2 may cause liver function damage, and liver functional abnormality after admission may be related to the use of lopinavir/ritonavir. Abnormal liver function is associated with prolonged hospital stay. These findings provide guidance for the clinical treatment of patients during the current pandemic.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Clinical Gastroenterology and Hepatology* at www.cghjournal.org, and at https://doi.org/10.1016/j.cgh.2012.11.00.

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Reprint requests
Address requests for reprints to: Zhanju Liu, MD, PhD, Department of Gastroenterology, Shanghai Tenth People's Hospital of Tongji University, Shanghai 200072, China. e-mail: liuzhanju88@126.com; fax: +86-21-66303983; or Jilin Cheng, MD, PhD, Department of Gastroenterology and Hepatology, Shanghai Public Health Clinical Center, Fudan University, Shanghai 201508, China; e-mail: chengjilin@shphc.org.cn; fax: +86-21-37990333.

CRediT Authorship Contributions
Zhanyu Fan (Data curation: Lead; Formal analysis: Equal; Investigation: Equal; Writing – original draft: Lead; Writing – review & editing: Equal)
Liping Chen (Formal analysis: Lead; Methodology: Lead; Supervision: Equal; Writing – original draft: Lead; Writing – review & editing: Equal)
Jun Li (Data curation: Supporting; Investigation: Supporting; Visualization: Supporting; Writing – original draft: Supporting)
Xin Cheng (Data curation: Supporting; Supervision: Supporting; Visualization:
Supporting; Writing – review & editing: Supporting)
Jingmao Yang (Methodology: Supporting; Writing – review & editing: Supporting)
Cheng Tian (Conceptualization: Supporting; Data curation: Supporting; Writing –
original draft: Supporting)
Yajun Zhang (Data curation: Supporting; Methodology: Supporting; Writing – original draft: Supporting)
Shaoping Huang (Conceptualization: Supporting; Writing – original draft: Supporting;
Writing – review & editing: Supporting)
Zhanju Liu (Conceptualization: Equal; Formal analysis: Supporting; Methodology:
Equal; Writing – review & editing: Lead)
Jilin Cheng (Conceptualization: Equal; Supervision: Lead; Visualization: Lead; Writing – review & editing: Equal)

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